

# When to biopsy Prostate Imaging and Data Reporting System version 2 (PI-RADSv2) assessment category 3 lesions? Use of clinical and imaging variables to predict cancer diagnosis at targeted biopsy

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Appendix available at [cuaj.ca](http://cuaj.ca)

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## Abstract

**Introduction:** We aimed to determine if clinical and imaging features can stratify men at higher risk for clinically significant (CS, International Society of Urological Pathology [ISUP] grade group  $\geq 2$ ) prostate cancer (PCa) in equivocal Prostate Imaging and Data Reporting System (PI-RADS) category 3 lesions on magnetic resonance imaging (MRI).

**Methods:** Approved by the institutional review board, this retrospective study involved 184 men with 198 lesions who underwent 3T-MRI and MRI-directed transrectal ultrasound biopsy for PI-RADS 3 lesions. Men were evaluated including clinical stage, prostate-specific antigen density (PSAD), indication, and MRI lesion size. Diagnoses for all men and by indication (no cancer, any PCa, CSpCa) were compared using multivariate logistic regression, including stage, PSAD, and lesion size.

**Results:** We found an overall PCa rate of 31.8% (63/198) and 10.1% (20/198) CSpCa (13 grade group 2, five group 3, and two group 4). Higher stage ( $p=0.001$ ), PSAD ( $p=0.007$ ), and lesion size ( $p=0.015$ ) were associated with CSpCa, with no association between CSpCa and age, PSA, or prostate volume ( $p>0.05$ ). PSAD modestly predicted CSpCa area under the curve (AUC) 0.66 (95% confidence interval [CI] 0.518–0.794) in all men and 0.64 (0.487–0.799) for those on active surveillance (AS). Model combining clinical stage, PSAD, and lesion size improved accuracy for all men and AS (AUC 0.82 [0.736–0.910],  $p<0.001$  and 0.785 [0.666–0.904],  $p<0.001$ ). In men with prior negative biopsy and persistent suspicion, PSAD (0.90 [0.767–1.000]) was not different

from the model ( $p>0.05$ ), with optimal cutpoint of  $\geq 0.215$  ng/mL/cc achieving sensitivity/specificity of 85.7/84.4%.

**Conclusions:** PI-RADSv2 category 3 lesions are often not CSpCa. PSAD predicted CSpCa in men with a prior negative biopsy; however, PSAD alone had limited value, and accuracy improved when using a model incorporating PSAD with clinical stage and MRI lesion size.

## Introduction

Prostate Imaging and Data Reporting System version 2 (PI-RADSv2) assessment categories positively correlate with an increased likelihood of detecting clinically significant prostate cancer (CSpCa) at targeted biopsy.<sup>1</sup> A PI-RADSv2 assessment category 3 (intermediate, clinically significant cancer likelihood equivocal) lesion is equivocal. Studies evaluating the likelihood of CSpCa cancer at targeted biopsy of PI-RADSv2 category 3 lesions have reported variable rates of PCa diagnosis, ranging from 5–30%, with the majority of studies showing a relatively low likelihood of eventual CSpCa diagnosis.<sup>2–4</sup> Management of PI-RADSv2 category 3 lesion is variable, ranging from immediate biopsy to surveillance.<sup>5,6</sup>

Given the disparity in management patterns for PI-RADSv2 category 3 lesions and a small but not insignificant proportion of these lesions harboring CSpCa, better classification of category 3 lesion is an unmet need. Previous studies in these patients have shown a correlation of CSpCa with older patient age, smaller prostate volumes, higher prostate-specific antigen density (PSAD), and increased clinical stage.<sup>7–11</sup> The purpose of this study was to evaluate a relatively large cohort of PI-RADSv2 category 3 lesions with histological confirmation to determine if clinical and imaging parameters could better delineate which category 3 lesions represent CSpCa and determine which patients should undergo targeted biopsy.

## Methods

This retrospective study was approved by the local institutional review board, who waived the need for patient informed consent. Between the dates of January 1, 2015 and September 1, 2018, we searched our electronic Picture Archiving and Communications System (PACS) for all magnetic resonance imaging (MRI)-directed transrectal ultrasound (TRUS) cognitive fusion targeted biopsies performed for category 3 lesions. A total of 397 patients with 412 reported category 3 lesions were identified. An experienced radiologist (having interpreted over 750 MRIs with PI-RADSv2) reviewed each MRI, blinded to histopathology results, and re-scored each lesion using PI-RADSv2, noting the location of each lesion using the using PI-RADSv2 sector map and using the peripheral zone (PZ) and transition zone (TZ) decision tree rules.<sup>12</sup> A total of 137 patients with 138 lesions were reclassified to a different PI-RADS categories and excluded, leaving 260 patients with 274 category 3 lesions. A total of 76 patients with 76 category 3 lesions were excluded due to inadequate imaging technique (i.e., without dynamic contrast enhancement, images with severe artifact [hip arthroplasties, rectal gas degrading image interpretation], etc.), prior treatment, or presence of prostate cancer in a different location than the target lesion. A summary of patient inclusion and exclusion criteria are provided in Fig. 1.

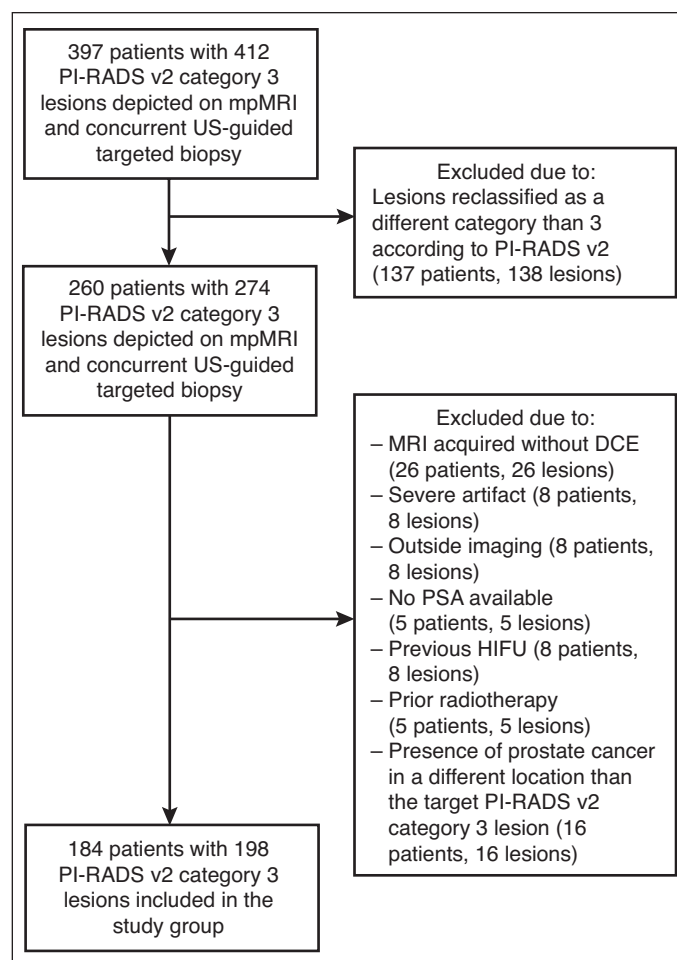
The clinical indication for MRI, patient age, PSA, prostate volume (measured on MRI using an ellipsoid volume calculation), and clinical stage (when available, recorded as T1c if there was negative digital rectal exam [DRE] and  $\geq$ T2 if positive DRE indicated by the referring physician) were recorded. PSAD was calculated by dividing the PSA by the MRI-calculated total prostate volume. Biopsy results from MRI-TRUS fusion targeted biopsy, including International Society of Urological Pathology (ISUP) grade group, were recorded.

## MRI technique and reporting

During the study period, prostate MRI was performed using a 3-Tesla MRI system (Philips Ingenia, Amsterdam, Netherlands). Details regarding the MRI protocols is summarized in Supplementary Table 1 (available at [cuaj.ca](http://cuaj.ca)). A standardized reporting template for prostate MRI was used.

## Targeted biopsy

Targeted biopsies were performed using TRUS guidance with cognitive fusion of MRI data onto real-time, 2-dimensional TRUS images. All ultrasound examinations were performed using modern ultrasound equipment (Phillips IU 22) and endocavity 5–9 Mhz end-fire probes. Biopsies were performed by a core group of three fellowship-trained abdom-



**Fig. 1.** Flow diagram showing patient selection used in this retrospective study. DCE: dynamic contrast enhancement; HIFU: high intensity focused ultrasound; mpMRI: multiparametric magnetic resonance imaging; PSA: prostate-specific antigen; US: ultrasound.

inal radiologists with mean of 8.3 years of experience (range 3–15) in cognitive fusion targeted biopsy of the prostate.

The TRUS-guided biopsy system used for all biopsies employed an 18-gauge, side-cutting needle. Biopsy were performed using standard technique, as previously described.<sup>13</sup> The cognitive fusion TRUS-guided biopsy reports specified: the target(s), the number of core biopsies performed per target (which is typically 3–5 biopsies<sup>14</sup>), and the specimen container into which targeted biopsies are placed. In this way, a biopsy result for each targeted lesion can be extracted from the histopathology report, which was done by the blinded radiologist after review of MRI.

## MRI lesion size measurement

The abdominal radiologist at time of initial database creation, blinded to other patient information and eventual histological diagnosis for each lesion, measured the size of lesion. For each lesion, the lesion was first classified as being located in either

the PZ or TZ based upon the PI-RADSv2 sector map. For lesion that crossed two zones, the epicenter of the lesion was used to determine the primary zonal origin. There were no central zone lesions in this cohort. The radiologist measured the single longest transverse dimension on axial ADC map images for PZ lesion and axial T2W for TZ lesion, where the lesion appeared the largest as described in PI-RADSv2 (Fig. 2).<sup>12</sup>

To assess for reproducibility of measurements, an abdominal radiologist with seven years of experience in prostate MRI (blinded) measured the size of tumor in a randomly selected 20% of lesions, a previously described reliable proportion of lesion needed to determine reproducibility of measurements.<sup>15</sup>

### Statistical analysis

Categorical data were tabulated and parametric data presented as mean  $\pm$  standard deviation (with range). Comparisons were performed between category 3 lesions with a benign diagnosis and those with any PCa diagnosis and CSPCa diagnosis using multivariate logistic regression. Statistical analysis was performed using SPSS v26.0 (SPSS inc., IBM Corp.). Empiric receiver operating characteristic (ROC) curves were con-

structed for each statistically significant variable associated with CSPCa, and also for a logistic regression model combining statistically significant variables. Area under the ROC curve (AUC) for each variable and for the logistic regression model were compared using ROC analysis and the optimal cutpoint that maximized sensitivity and specificity determined using the method described by Youden.

## Results

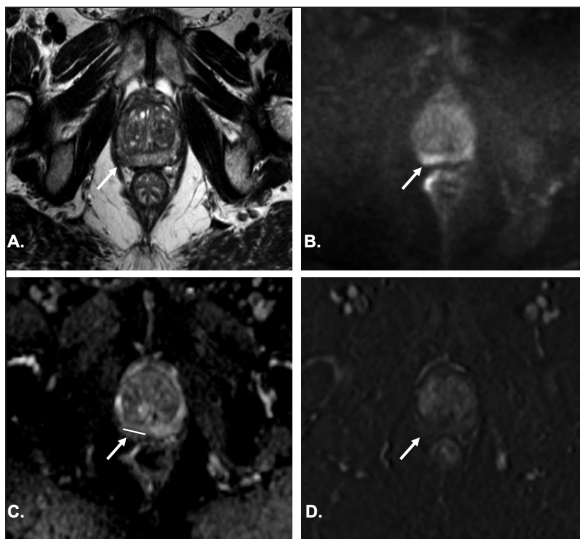
### All patients

Patient demographic and clinical data are presented in Table 1. The mean patient age, PSA and PSAD were  $63.36 \pm 8.43$  years,  $9.37 \pm 6.52$  (range 0.79–36.25) ng/mL, and  $0.168 \pm 0.117$  (range 0.019–0.995) ng/mL/cc, respectively. A total of 81.0% (149/184) patients had clinical staging data from DRE available, with 77.2% (115/149) negative or T1c and 22.8% (34/149)  $\geq$ T2a results.

From the 198 PI-RADSv2 category 3 MRI lesions, any PCa diagnosis was established in 32% (63/198) of biopsies, whereas CSPCa was diagnosed in only 10% (20/198) of biopsies. Of the 20 CSPCa diagnoses, ISUP grade groups were: ISUP 2, n=13; ISUP 3, n=5; ISUP 4, n=2. MRI lesions were fairly evenly split between the PZ (54.0%, 107/198) and TZ (46.0%, 91/198); however, 30.0% (6/20) of CSPCa were located in the PZ and 70.0% (14/20) CSPCa were located in the TZ. The mean lesion size was  $12.7 \pm 5.4$  mm overall,  $11.1 \pm 4.2$  mm for lesions in the PZ, and  $15.0 \pm 5.5$  mm for lesions in the TZ ( $p < 0.001$ ).

There was no association between age or PSA and CSPCa diagnosis ( $p = 0.073$ ,  $0.591$ , respectively); however, patients with any PCa diagnosis had lower PSA compared to those with benign histology ( $10.1 \pm 7.1$  vs.  $7.9 \pm 5.0$  ng/mL,  $p = 0.030$ ) (Table 1). Both patients with any PCa and CSPCa diagnoses had higher clinical stage ( $p = 0.027$  and  $0.001$ , respectively) at DRE. Mean prostate volume was  $64.95 \pm 42.69$  (range 18–324) mL. There was a trend with CSPCa diagnosis occurring in smaller prostate volumes ( $66.9 \pm 44.25$  mL vs.  $49.1 \pm 21.4$  mL,  $p = 0.078$ ); however, the difference was not significant (Table 1). PSAD was significantly higher in patients with category 3 lesions that yielded CSPCa compared to patients with benign histology and any PCa diagnosis ( $0.234 \pm 0.151$  ng/mL/cc vs.  $0.160 \pm 0.111$  ng/mL/cc,  $p = 0.007$ ). Category 3 lesions that yielded any PCa and CSPCa were significantly larger ( $14.0 \pm 5.2$  mm and  $14.9 \pm 3.3$  mm vs.  $12.4 \pm 5.2$  mm,  $p = 0.047$  and  $0.015$ , respectively) than those with benign histology. With respect to reproducibility of measurements, size measurements did not differ between observers ( $p = 0.592$ ).

The AUC for the diagnosis of CSPCa using clinical stage, PSAD and, largest tumor size per patient evaluated independently were:  $0.671$  (95% confidence interval [CI]  $0.529$ – $0.812$ ),



**Fig. 2** 67-year-old male on active surveillance (AS) with a Prostate Imaging and Data Reporting System (PI-RADS) 3 lesion in the right mid peripheral zone (PZ) yielding clinically significant prostate cancer (CSPCa) Gleason 3+4 (International Society of Urological Pathology [ISUP] grade group 2) at targeted biopsy. **(A)** Axial T2-weighted (T2W) magnetic resonance imaging (MRI) shows a non-circumscribed moderately hypointense observation (arrow). **(B)** Axial b1600 mm<sup>2</sup>/sec diffusion weighted image shows mild-to-moderately high signal intensity in the lesion (arrow). **(C)** Axial apparent diffusion coefficient (ADC) map image shows only corresponding iso- or hypointense signal intensity (arrow). **(D)** Subtracted dynamic contrast enhance demonstrate no focal early enhancement, classified as a PI-RADS 3 lesion. White line in **(C)** indicates method of observation size measurement (14 mm) performed on ADC maps for peripheral zone lesions and T2W for transition zone lesions.



**Table 1. Comparison of categorical and parametric data between PI-RADSv2.1 assessment category 3 lesions with targeted biopsy showing benign, any prostate cancer and significant (ISUP  $\geq 2$ ) prostate cancer in 198 PI-RADS 3 lesions in 184 patients that underwent cognitive fusion MRI-transrectal ultrasound-targeted biopsy**

	Benign histology (n=123)	Any cancer diagnosis (n=61)	p <sup>1</sup>	Clinically significant cancer diagnosis (n=20)	p <sup>2</sup>
Age (years)	63.1 $\pm$ 8.7	64.0 $\pm$ 7.9	0.484	66.6 $\pm$ 8.2	0.073
PSA <sup>3</sup> (ng/mL)	10.1 $\pm$ 7.1	7.9 $\pm$ 5.0	0.030	10.1 $\pm$ 6.5	0.591
Clinical stage, when available <sup>4</sup>			0.027		0.001
T1c	83.3% (75/90)	67.8% (40/59)		47.4% (9/19)	
$\geq$ T2	16.7% (15/90)	32.2% (19/59)		55.6% (10/19)	
Indication			<0.001		0.023
On AS	26.0% (32/123)	72.1% (44/61)		65.0% (13/20)	
Negative prior biopsy	74.0% (91/123)	27.9% (17/61)		35.0% (7/20)	
Prostate volume (mL)	67.7 $\pm$ 44.1	59.4 $\pm$ 39.4	0.219	49.1 $\pm$ 21.4	0.078
PSA density (ng/mL/cc)	0.171 $\pm$ 0.119	0.163 $\pm$ 0.116	0.630	0.234 $\pm$ 0.151	0.007
Lesion size <sup>5</sup> (mm)	12.4 $\pm$ 5.2	14.0 $\pm$ 5.2	0.047	14.9 $\pm$ 3.3	0.015
Lesion location			0.122		0.023
Peripheral zone	57.8% (78/135)	46.0% (29/63)		30.0% (6/20)	
Transition zone	42.2% (57/135)	54.0% (34/63)		70.0% (14/20)	

<sup>1</sup>Comparison performed between lesions with benign histology and any cancer diagnosis. <sup>2</sup>Comparison performed between lesions with benign and non-significant histology and clinically significant cancer diagnosis. <sup>3</sup>Prostate serum antigen. <sup>4</sup>Total of 149 patient had clinical stage available. Clinical stage compared on a per patient and not per lesions level. <sup>5</sup>Analysis on a per-lesions bases. Total of 135 lesions with benign histology, 43 lesions with ISUP group 1 histology, and 20 with clinically significant ISUP  $\geq 2$  cancer. AS: active surveillance; ISUP: International Society of Urological Pathology; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

0.698 (0.570–0.826), and 0.675 (0.582–0.768), respectively. A logistic regression model combining these three variables achieved an improved AUC for diagnosis of CSpCa diagnosis of 0.823 (0.737–0.910,  $p < 0.001$ ) (Fig. 3).

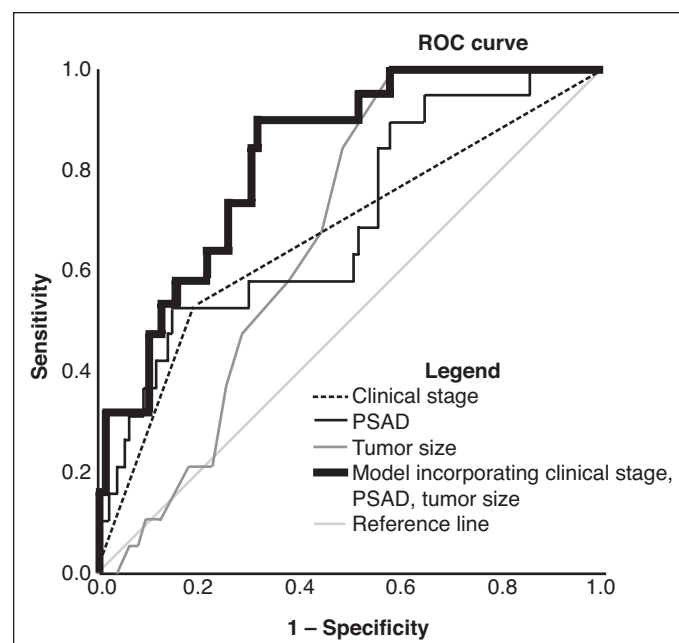
### Subgroup of men on active surveillance

Subgroup analyses in men undergoing MRI performed for active surveillance (AS) are presented in Table 2. Notably, in MRI performed for AS, there was a trend towards CSpCa cancers having higher clinical stage; however, the results were not significant ( $p = 0.056$ ). Category 3 lesions that yielded CSpCa were larger ( $p = 0.028$ ). There was no association between PSAD and CSpCa ( $p = 0.308$ ). In patients being evaluated on AS, AUCs for diagnosis of CSpCa using clinical stage, PSAD, and largest tumor size per patient were 0.637 (0.453–0.821), 0.643 (0.487–0.799), and 0.701 (0.574–0.829), respectively. The logistic regression model combining all three features improved the AUC to 0.785 (0.666–0.904,  $p < 0.001$ ) (Fig. 4).

### Subgroup of on men with prior negative template biopsy and persistent suspicion

Data on men undergoing MRI with prior negative template biopsy but persistent clinical suspicion of PCa are presented in Table 3. Notably, patients with CSpCa had higher PSAD and clinical stage at DRE ( $p = 0.0001$  and 0.007, respectively). There was no association between size and CSpCa ( $p = 0.688$ ). In men undergoing MRI for prior negative biopsy but persisting clinical suspicion of cancer, AUCs for diagnosis of CSpCa using clinical stage, PSAD, and largest tumor size per patient were 0.708 (0.482–0.934), 0.898 (0.805–

0.991), and 0.605 (0.470–0.739), respectively. The logistic regression model combining all three variables achieved an AUC of 0.892 (0.767–1.000), which was not improved compared to PSAD alone ( $p > 0.05$ ) (Fig. 5). The optimal cutpoint that maximized the diagnostic accuracy for CSpCa diagnosis in this cohort of men was  $\geq 0.215$  ng/mL/cc, achieving a sensitivity and specificity of 85.7% and 84.4%, respectively.



**Fig. 3.** Receiver operator characteristic (ROC) curve depicting accuracy for diagnosis of any significant prostate cancer among Prostate Imaging and Data Reporting System version 2 (PI-RADSv2) assessment category 3 lesions using a logistic regression model combining patient clinical stage, prostate-specific antigen density (PSAD), and larger tumor volume for all patients.

**Table 2. Subgroup analysis for patients on active surveillance and PI-RADSv2.1 assessment category 3 lesions with targeted biopsy showing benign, any prostate cancer and significant (ISUP  $\geq 2$ ) prostate cancer in 82 PI-RADS 3 lesions in 76 patients that underwent cognitive fusion MRI-transrectal ultrasound-targeted biopsy**

	Benign histology (n=36)	Any cancer diagnosis (n=33)	p <sup>1</sup>	Clinically significant cancer diagnosis (n=13)	p <sup>2</sup>
Age (years)	66.6 $\pm$ 10.2	63.3 $\pm$ 7.9	0.113	66.8 $\pm$ 9.2	0.353
PSA <sup>3</sup> (ng/mL)	9.84 $\pm$ 7.04	7.04 $\pm$ 4.44	0.034	8.56 $\pm$ 6.70	0.800
Clinical stage, when available <sup>4</sup>			0.957		0.056
T1	72.7% (16/22)	72.1% (31/43)		50.0% (6/12)	
$\geq$ T2	27.3% (6/22)	27.9% (12/43)		50.0% (6/12)	
Prostate volume (mL)	75.16 $\pm$ 54.17	60.93 $\pm$ 42.68	0.204	53.26 $\pm$ 21.34	0.263
PSA density (ng/mL/cc)	0.155 $\pm$ .097	0.136 $\pm$ 0.079	0.341	0.167 $\pm$ 0.096	0.308
Lesion size <sup>5</sup> (mm)	13.3 $\pm$ 4.9	13.6 $\pm$ 4.9	0.817	15.7 $\pm$ 3.4	0.028
Lesion location <sup>5</sup>			0.418		0.162
Peripheral zone	61.1% (22/36)	52.2% (24/46)		38.5% (5/13)	
Transition zone	38.9% (14/36)	47.8% (20/46)		61.5% (8/13)	

<sup>1</sup>Comparison performed between lesions with benign histology and any cancer diagnosis. <sup>2</sup>Comparison performed between lesions with benign and non-significant histology and clinically significant cancer diagnosis. <sup>3</sup>Prostate serum antigen. <sup>4</sup>Total of 65 patient had clinical stage available. Clinical stage compared on a per patient and not per lesions level. <sup>5</sup>Analysis on a per-lesion bases for a total of 76 lesions. Total of 36 lesions with benign histology, 33 lesions with ISUP group 1 histology, and 13 with clinically significant ISUP  $\geq 2$  cancer. ISUP: International Society of Urological Pathology; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

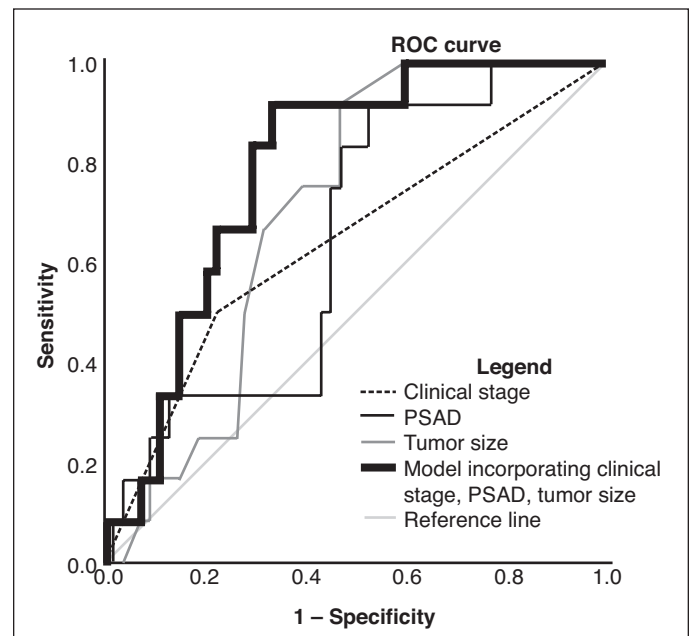
## Discussion

In this study, the overall rate of PI-RADSv2 category 3 lesions harboring CSPCa was approximately one in 10. We identified clinical and imaging features that were predictive of CSPCa, including higher clinical stage at DRE, higher PSAD, and larger MRI lesion size. Overall, these variables performed modestly for predicting CSPCa at targeted biopsy; however, a logistic regression model combining all three variables had high accuracy for diagnosis of CSPCa. This model was particularly useful in the AS cohort within our study. In men undergoing MRI due to persistent clinical suspicion and prior negative template biopsy, PSAD was much more valuable for predicting CSPCa diagnosis at targeted biopsy and had similar high accuracy compared to the logistic regression model.

Higher PSAD has been shown to be a predictor of CSPCa cancer and is a widely evaluated biomarker.<sup>4,7-10,16,17</sup> PI-RADS 3 lesions are indeterminate and, currently, there is no consensus on the optimal management.<sup>5,6</sup> It has been proposed that patients with lower PSAD values ( $\leq 0.10$ – $0.15$  ng/mL/cc) and PI-RADS category 3 lesions could be safely managed with close surveillance.<sup>4,9,10</sup> For example, Gortz et al found that using a PSAD  $< 0.10$  ng/mL/cc, 43% (43/101) of biopsy-naïve men could be spared a biopsy with only 2% (1/43) risk of missing CSPCa.<sup>9</sup> Higher detection rates of CSPCa have been found when stratifying according to higher PSAD values ( $> 0.30$  ng/mL/cc), however, at a risk of missing a proportion of CSPCa.<sup>10</sup> The optimal cutpoint in patients with persistent high risk after negative biopsy found in our study is higher than the proposed cutpoints of  $\leq 0.15$  ng/mL/cc.<sup>4,10,11,16,18</sup> The cutpoint used in clinical practice will need to balance the risk and benefits of potential biopsy with missing a cancer if surveillance is chosen.

Other clinical and imaging biomarkers have shown promise at predicting CSPCa, including clinical stage and

MRI lesion size.<sup>7,8,11</sup> Our findings of higher clinical stage in patients with CSPCa are consistent with the current recommendations that DRE should be offered during the initial risk assessment of a patient with disease.<sup>19</sup> We found that larger tumor size was predictive of any PCa and CSPCa, which is consistent with data demonstrating that larger tumors are associated with more aggressive disease.<sup>20,21</sup> There are no other studies that have showed an association between category 3 lesions size and cancer diagnosis



**Fig. 4.** Receiver operator characteristic (ROC) curve depicting accuracy for diagnosis of any significant prostate cancer among Prostate Imaging and Data Reporting System version 2 (PI-RADSv2) assessment category 3 lesions using a logistic regression model combining patient clinical stage, prostate-specific antigen density (PSAD), and larger tumor volume for patients being managed with active surveillance (AS).

**Table 3. Subgroup analysis for patients with negative prior biopsy and PI-RADSv2.1 assessment category 3 lesion with targeted biopsy showing benign, any prostate cancer and significant (ISUP  $\geq 2$ ) prostate cancer in 116 PI-RADS 3 lesion in 108 patients that underwent cognitive fusion MRI-transrectal ultrasound-targeted biopsy**

	Benign histology (n=91)	Any cancer diagnosis (n=17)	p <sup>1</sup>	Clinically significant cancer diagnosis (n=7)	p <sup>2</sup>
Age (years)	61.8 $\pm$ 7.8	65.9 $\pm$ 7.7	0.052	66.1 $\pm$ 6.5	0.206
PSA <sup>3</sup> (ng/mL)	10.2 $\pm$ 7.1	10.3 $\pm$ 5.7	0.975	13.0 $\pm$ 5.2	0.268
Clinical stage, when available <sup>4</sup>			0.005		0.007
T1	86.8% (59/84)	56.3% (9/16)		42.9% (3/7)	
$\geq$ T2	13.2% (9/84)	43.8% (7/16)		57.1% (4/7)	
Prostate volume (mL)	65.04 $\pm$ 40.06	55.56 $\pm$ 29.91	0.356	41.2 $\pm$ 20.7	0.115
PSA density (ng/mL/cc)	0.177 $\pm$ 0.123	0.231 $\pm$ 0.163	0.124	0.360 $\pm$ 0.158	0.0001
Lesion size <sup>5</sup> (mm)	12.1 $\pm$ 5.3	15.0 $\pm$ 5.9	0.038	13.3 $\pm$ 2.7	0.688
Lesion location <sup>5</sup>			0.038		0.036
Peripheral zone	56.6% (56/99)	29.4% (5/17)		14.3% (1/7)	
Transition zone	43.4% (43/99)	70.6% (12/17)		85.7% (6/7)	

<sup>1</sup>Comparison performed between lesions with benign histology and any cancer diagnosis. <sup>2</sup>Comparison performed between lesions with benign and non-significant histology and clinically significant cancer diagnosis. <sup>3</sup>Prostate serum antigen. <sup>4</sup>Total of 84 patient had clinical stage available. Clinical stage compared on a per patient and not per lesion level. <sup>5</sup>Analysis on a per-lesions bases for a total of 116 lesions. Total of 91 lesions with benign histology, 10 lesions with ISUP group 1 histology, and 7 with clinically significant ISUP  $\geq 2$  cancer. ISUP: International Society of Urological Pathology; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

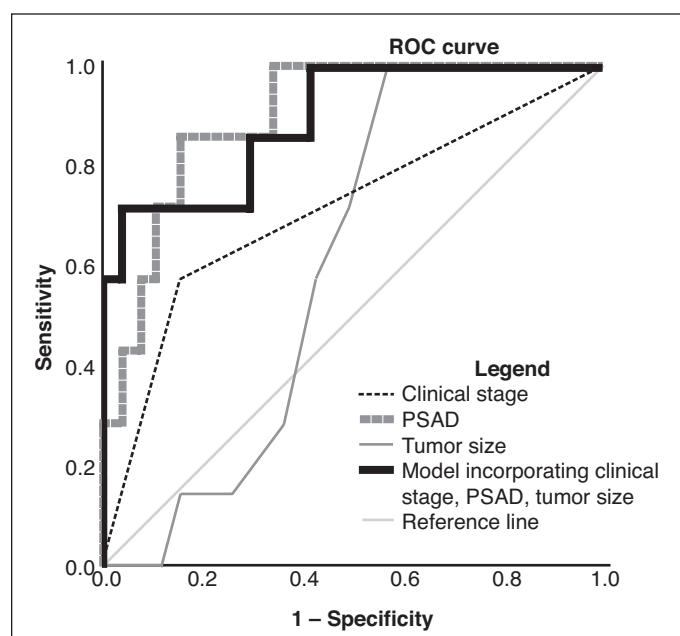
at biopsy, and other studies that have evaluated PI-RADS 3 lesions found no significant differences in relation to tumor size.<sup>7,8,11</sup> The present study had the largest sample size, which may account for the significance results of tumor size; however, further studies are needed to validate our results. Other features associated with CSPCa, including smaller prostate volume, higher PSA, and older age,<sup>8,11</sup> may present as lesions categorized as category 4 or 5 and may

have been excluded from our study. We did not evaluate other clinical or imaging features, such as PSA kinetics or quantitative diffusion imaging metrics, and further larger, multi-institutional studies evaluating all biomarkers would be of interest to improve detection of CSPCa.

The patient population and indication for MRI has been shown to affect the rates of cancer diagnosis.<sup>4,22</sup> When evaluating men on AS, our model incorporating the significant features (including clinical stage, PSAD, and lesion size) improved the accuracy at determining which patients may have CSPCa at MRI-directed targeted biopsy. However, when evaluating patients with persistent clinical suspicion after negative biopsy, PSAD was the single best feature at determining malignancy. These findings suggest that the optimal PSAD cutpoint will be different between groups. This reasoning is supported by extrapolation of data from the systematic review and meta-analysis by Maggi et al, which found differences in any cancer rates between patients who had previous negative biopsy and biopsy-naïve men ( $p < 0.001$ ).<sup>4</sup> With the increased use of MRI, MRI-directed biopsy in biopsy-naïve men is being explored, and as the cancer rates differ in this subset of patients,<sup>4,23</sup> further work evaluating clinical and imaging predictive factors by MRI indication is of interest.

## Limitations

There are limitations of our study. Despite the large sample size of PI-RADS category 3 lesions and although the rates of malignancy in our study are comparable to those reported in the literature,<sup>4</sup> the number of significant cancers remains small, which limits analysis. This was a retrospective analysis from a single tertiary care referral center, which may introduce selection bias into our results. MRI-directed targeted biopsy, the comparator in this study, is limited if the



**Fig. 5.** Receiver operator characteristic (ROC) curve depicting accuracy for diagnosis of any significant prostate cancer among Prostate Imaging and Data Reporting System version 2 (PI-RADSv2) assessment category 3 lesions using a logistic regression model combining patient clinical stage, prostate-specific antigen density (PSAD), and larger tumor volume for patients with persistent clinical concern and negative prior biopsy.

tumor was missed and not adequately sampled. This may have been exacerbated by our targeting method, cognitive fusion, as some literature suggests higher targeting accuracies with software fusion or in-bore MRI-guided targeting. Results from the recent prospective FUTURE trial indicate no preferential advantage between any of the aforementioned targeting methods that were all used in the recent landmark PROMIS and PRECISION trials assessing targeted biopsy for prostate cancer diagnosis.<sup>24-26</sup> Therefore, even if small differences exist among the various methods of performing targeted prostate biopsy, our results reflect the current state of biopsy in clinical practice, with similar results to those obtained using other methods of targeting category 3 lesions.

## Conclusions

Our study demonstrates that among equivocal PI-RADSv2 category 3 lesions, CSPCa is uncommon, occurring in approximately 10% of targeted biopsies. Higher clinical stage at DRE, higher PSAD, and larger tumors size measured on MRI are useful features associated with eventual CSPCa diagnosis at targeted biopsy. In men undergoing MRI for AS, a logistic regression model incorporating all these features was highly accurate at predicting CSPCa diagnosis and significantly improved accuracy of classification compared to each feature assessed independently. In men with persistent clinical suspicion of PCa and negative prior biopsy, PSAD was more valuable and showed similar high accuracy compared to the logistic regression model for prediction of CSPCa at targeted biopsy. A higher reported cutpoint of  $\geq 0.215$  ng/mL/cc optimized accuracy of classification in our study. Large-scale, prospective evaluation of imaging and clinical variables in all patient populations are required. Models incorporating features described in the present study and in prior studies to improve stratification of category 3 lesions require validation.

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